

*cont*

*C 1*

*Sub D<sup>1</sup> Cont*

alkyl; or C<sub>1</sub>-C<sub>4</sub> alkanoyl;

R<sup>12</sup> is H; C<sub>1</sub>-C<sub>6</sub> alkyl; (C<sub>1</sub>-C<sub>3</sub> alkoxy)C<sub>2</sub>-C<sub>6</sub> alkyl; (hydroxy)C<sub>2</sub>-C<sub>6</sub> alkyl; (R<sup>13</sup>R<sup>14</sup>N)C<sub>2</sub>-C<sub>6</sub> alkyl; (R<sup>13</sup>R<sup>14</sup>NOC)C<sub>1</sub>-C<sub>6</sub> alkyl; CONR<sup>13</sup>R<sup>14</sup>; CSNR<sup>13</sup>R<sup>14</sup>; or C(NH)NR<sup>13</sup>R<sup>14</sup>; and

R<sup>13</sup> and R<sup>14</sup> are each independently H; C<sub>1</sub>-C<sub>4</sub> alkyl; (C<sub>1</sub>-C<sub>3</sub> alkoxy)C<sub>2</sub>-C<sub>4</sub> alkyl; or (hydroxy)C<sub>2</sub>-C<sub>4</sub> alkyl;  
or a pharmaceutically acceptable salt thereof;  
or a pharmaceutical composition containing either entity.

*C 2*

*Sub D<sup>1</sup> Cont*

5. A method of treating sexual dysfunction due to trauma and/or nerve damage which accompanies a spinal cord injury in an animal, comprising administering to an animal in need of such treatment an effective amount of sildenafil, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity

#### REMARKS

Claims 1 and 5 have been amended to make it clear that the condition of sexual dysfunction being treated in an animal is due to trauma and/or nerve damage which accompany a spinal cord injury in the animal. Support for the amendment is at page 3, lines 12-13.

Claims 1, 2, 5-10 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12-36 of co-pending Application No. 08/549,792, in view of Tay et al. (Medline Abstract, AN 96186389), Beretta et al. (Medline Abstract, AN 94136073) and Chancellor et al. (Medline Abstract, AN 94182317).

For the sake of completeness, Applicants note that co-pending Application No. 08/549,792 issued on October 22, 2002 as US patent No. 6,469,012. In the rejection, the Examiner stated, *inter alia*, that

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the U.S. Application Serial No. 08/549,792, similar to the instant claims, are drawn to methods of treating sexual dysfunction broadly and male erectile dysfunction.

U.S. Application Serial No. 08/549,792 does not expressly claim the treated subject is with injured spinal cord.

However, Tay et al. teaches that erectile dysfunction caused by injured spinal cord may be psychogenic, not organic. See the abstract.

Beretta et al. and Chancellor et al. teach that vasoactive compounds are known to be useful for treatment of erectile dysfunction in men with injured spinal cord. See the abstracts.

Therefore, it would have been *prima facie* obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to employ the vasoactive compounds herein for the treatment of ED in men with spinal cord injury, including those who exhibits essentially no residual erectile function. [Pages 2-3 of the Office Action]

The rejection is traversed on the basis that the references are legally insufficient to support the double patenting rejection. Applicants note it is not completely clear how the Examiner intended for Tay to fit into the rejection. In any case, because Tay appears to have been cited for its disclosure of psychogenic impotence, and because Applicants have now amended their claims to state that the spinal cord injury is due to trauma and/or nerve damage which accompanies a spinal cord injury in an animal, it is believed that Tay is inapplicable and/or moot with respect to the amended claims.

The Examiner otherwise appeared to summarize the rejection on page 3, 3<sup>rd</sup> full paragraph (i.e., at lines 7-10). Paraphrasing, the Examiner characterized the secondary references (presumably Chancellor and Beretta) as showing that vasoactive compounds are known to be useful for the treatment of ED in men with spinal cord injury, including those who exhibit essentially no erectile dysfunction. Presumably, the Examiner is referring to the testing of minoxidil, and papaverine in the Chancellor Abstract, and minoxidil in the Beretta abstract, as to their erectile effects in spinal cord injured (SCI) men. Interestingly, the prior art seems to create a state of confusion regarding whether minoxidil works or not. Note in particular the Chancellor article states that minoxidil

“...induced no change in rigidity (range 0-15%)...Both subjective and objective erectile responses to minoxidil were poor...”

Further, Beretta and Chancellor fail to suggest or disclose anything relating to whether the different compounds of the instant invention would be useful for the treatment of SCI men. The secondary references are simple anecdotal accounts of the effectiveness of minoxidil and papaverine in the

treatment of erectile dysfunction in SCI men. But the reference compounds are different from the compounds to which claims 1-2 are limited. Neither of them is related to sildenafil to which claims 5-10 are limited and, as previously noted, neither of them makes any suggestion with respect to any other compounds outside the ones they disclose. The law is very clear in respect of references such as Beretta and Chancellor. To be effective in supporting an obviousness rejection, the references must somehow (1) suggest doing that which Applicants have done and (2) provide a reasonable expectation of success. If they do not, then the best one can say is that they may (or may not) render an invention "obvious to try". But, the law is emphatic that "obvious to try" is NOT the test of obviousness under 35 U.S.C. §103. American Hospital Supply Corp. v. Travenol Laboratories, Inc., 223 USPQ 577, 582 (Fed. Cir. 1984). The Federal Circuit has explained the proper test:

The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out **and would have a reasonable likelihood of success**, viewed in light of the prior art. **Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure** (emphasis added).

In re Dow Chemical Co., 5 USPQ.2d 1529, 1531 (Fed. Cir. 1988); Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd. 18 USPQ.2d 1016, 1022-23 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). Neither a suggestion of the dosage form itself nor any likelihood of success (i.e., of providing any benefit) would be expected based on Beretta, and Chancellor.

Clearly, the references are insufficient to support the rejection. It is accordingly respectfully requested that the rejection be withdrawn.

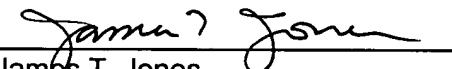
Claims 1, 2, and 5-10 stand rejected under 35 USC 103(a) as being unpatentable over WO 94/28902 in view of Tay, Beretta and Chancellor. The rejection appears to be completely analogous to the double patenting rejection, except that in place of the application 08/549,792, the WO, which is the published version of the corresponding European application, has been substituted.

The rejection is traversed on the same basis as presented above for the double patenting rejection, and Applicants' comments from above are incorporated herein in that regard.

As previously noted by the Examiner in respect of application no. 08/549,792, the WO document discloses that the instant compounds are useful for the treatment of sexual dysfunction, but fails to disclose anything regarding the treatment of sexual dysfunction in an SCI animal. Applicants' comments in relation to Chancellor and Beretta are the same. That is, notwithstanding the fact that these references disclose one or more purportedly vasoactive compounds, neither suggests anything in relation to the instant compounds, including sildenafil. These references cannot be said to supply a suggestion to do that which Applicants have invented using Applicants' different compounds, and certainly neither reference supplies the requisite expectation of success required by law. Any applicability that Tay may have had to the rejection is moot in view of Applicants' amendments to the claims.

In view of the foregoing comments and amendments, this case is believed to be in condition for allowance, and a Notice of Allowance is courteously solicited.

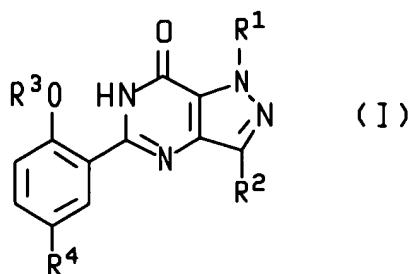
Date: October 23, 2002

  
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VERSION MARKED UP TO SHOW CHANGES MADE

1. A method of treating sexual dysfunction due to trauma and/or nerve damage which accompanies a spinal cord injury in an animal [with an injured spinal cord], comprising administering to an animal in need of such treatment an effective amount of a compound of formula (I):



wherein:

$R^1$  is H; C<sub>1</sub>-C<sub>3</sub> alkyl; C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl; or C<sub>3</sub>-C<sub>5</sub> cycloalkyl;

$R^2$  is H; C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with C<sub>3</sub>-C<sub>6</sub> cycloalkyl; C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl; or C<sub>3</sub>-C<sub>6</sub> cycloalkyl;

$R^3$  is C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with C<sub>3</sub>-C<sub>6</sub> cycloalkyl; C<sub>1</sub>-C<sub>6</sub> perfluoroalkyl; C<sub>3</sub>-C<sub>5</sub> cycloalkyl; C<sub>3</sub>-C<sub>6</sub> alkenyl; or C<sub>3</sub>-C<sub>6</sub> alkynyl;

$R^4$  is C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with OH, NR<sup>5</sup>R<sup>6</sup>, CN, CONR<sup>5</sup>R<sup>6</sup> or CO<sub>2</sub>R<sup>7</sup>; C<sub>2</sub>-C<sub>4</sub> alkenyl optionally substituted with CN, CONR<sup>5</sup>R<sup>6</sup> or CO<sub>2</sub>R<sup>7</sup>; C<sub>2</sub>-C<sub>4</sub> alkanoyl optionally substituted with NR<sup>5</sup>R<sup>6</sup>; (hydroxy)C<sub>2</sub>-C<sub>4</sub> alkyl optionally substituted with NR<sup>5</sup>R<sup>6</sup>; (C<sub>2</sub>-C<sub>3</sub> alkoxy)C<sub>1</sub>-C<sub>2</sub> alkyl optionally substituted with OH or NR<sup>5</sup>R<sup>6</sup>; CONR<sup>5</sup>R<sup>6</sup>; CO<sub>2</sub>R<sup>7</sup>; halo; NR<sup>5</sup>R<sup>6</sup>; NHSO<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>; NHSO<sub>2</sub>R<sup>8</sup>; SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup>; or phenyl, pyridyl, pyrimidinyl, imidazolyl, oxazolyl, thiazolyl, thienyl or triazolyl any of which is optionally substituted with methyl;

$R^5$  and  $R^6$  are each independently H or C<sub>1</sub>-C<sub>4</sub> alkyl, or together with the

nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino, 4-N(R<sup>11</sup>)-piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or OH;

R<sup>7</sup> is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>8</sup> is C<sub>1</sub>-C<sub>3</sub> alkyl optionally substituted with NR<sup>5</sup>R<sup>6</sup>;

R<sup>9</sup> and R<sup>10</sup> together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino or 4-N(R<sup>12</sup>)-piperazinyl group wherein said group is optionally substituted with C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy, NR<sup>13</sup>R<sup>14</sup> or CONR<sup>13</sup>R<sup>14</sup>;

R<sup>11</sup> is H; C<sub>1</sub>-C<sub>3</sub> alkyl optionally substituted with phenyl; (hydroxy)C<sub>2</sub>-C<sub>3</sub> alkyl; or C<sub>1</sub>-C<sub>4</sub> alkanoyl;

R<sup>12</sup> is H; C<sub>1</sub>-C<sub>6</sub> alkyl; (C<sub>1</sub>-C<sub>3</sub> alkoxy)C<sub>2</sub>-C<sub>6</sub> alkyl; (hydroxy)C<sub>2</sub>-C<sub>6</sub> alkyl; (R<sup>13</sup>R<sup>14</sup>N)C<sub>2</sub>-C<sub>6</sub> alkyl; (R<sup>13</sup>R<sup>14</sup>NOC)C<sub>1</sub>-C<sub>6</sub> alkyl; CONR<sup>13</sup>R<sup>14</sup>; CSNR<sup>13</sup>R<sup>14</sup>; or C(NH)NR<sup>13</sup>R<sup>14</sup>; and

R<sup>13</sup> and R<sup>14</sup> are each independently H; C<sub>1</sub>-C<sub>4</sub> alkyl; (C<sub>1</sub>-C<sub>3</sub> alkoxy)C<sub>2</sub>-C<sub>4</sub> alkyl; or (hydroxy)C<sub>2</sub>-C<sub>4</sub> alkyl;

or a pharmaceutically acceptable salt thereof;

or a pharmaceutical composition containing either entity.

5. A method of treating sexual dysfunction due to trauma and/or nerve damage which accompanies spinal cord injury in an animal[ with an injured spinal cord], comprising administering to an animal in need of such treatment an effective amount of sildenafil, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity.